REMARKS

Claims 28-46 are pending in the application. By virtue of this amendment, claims 28, 31, 3, 44 and 46 are amended.

Support for the amendments to claim 28 can be found *inter alia* on page 2, lines 14-20, page 2, line 27 to page 3, line 5, page 3, lines 12-13, page 6, lines 10-11, page 6, lines 5-7, page 12, lines 5-7, page 4, lines 9-10, page 5, lines 9-11, page 6, lines 12-14, and page 15, lines 8-11 of the Specification. Support for the amendment to claim 31 can be found *inter alia* on page 5, lines 28-30. Support for the amendment to claim 36 can be found *inter alia* on page 7, line 30 to page 8, line 33. Support for the amendment to claim 44 can be found *inter alia* on page 5, lines 28-30. Support for the amendment to claim 46 can be found *inter alia* on page 5, lines 9-11, page 6, lines 12-14, and page 15, lines 8-11.

No new matter is added. Entry of the amendments is respectfully requested.

Reconsideration is respectfully requested in view of the above amendments and following remarks. For the Examiner's convenience and reference, Applicants' remarks are presented in the order in which the corresponding issues were raised in the Office Action.

Claim rejections under 35 U.S.C. § 112

Claims 28-46 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(i) The Examiner finds the recitation of a mammal in claim 28 to be indefinite because the relationship between the multiple individuals and the mammal of step (2) is undefined. In response, Applicants amend claim 28 to delete "mammal" and specify "the individual" in step (2). Applicants respectfully submit that this amendment renders the claim no longer indefinite.

(ii) The Examiner finds claim 28 to be indefinite because the claimed method does not recite steps for genotyping multiple samples. The Examiner also finds claim 28 to be indefinite

because it is unclear whether and/or how simultaneous genotyping is accomplished because the method steps do not recite simultaneous detection and/or genotyping.

In response, Applicants amend claim 28 to specify "the formation of a hybrid or lack of formation of a hybrid after a single round of hybridization at the distinct location is indicative of a genotype of the individual." Claim 28 further specifies "a microarray of polynucleotide samples from multiple individuals" wherein the microarray contains "a plurality of samples containing genotypes of interest with each sample in a distinct location." Claim 28 further specifies probe mixtures having sequences "specifically complementary ... for each sample for which a genotype is to be determined."

Applicants submit that claim 28, as amended, specifies multiple samples each at a distinct location and representative of a genotype, wherein hybridization (or lack thereof) of the specified probe mixture at each distinct location "is indicative of a genotype of the individual." Since the specified "microarray contains a plurality of samples," claim 28 specifies simultaneous genotyping of multiple samples. Withdrawal of this ground for rejection is respectfully requested.

(iii) The Examiner finds the recitation of "array" in claim 28(d) to lack proper antecedent basis. Claim 28(d) has been amended to delete reference to "the array" and specify "the microarray" Applicants submit that "the microarray" has antecedent basis in step "1" of the claim and respectfully request withdrawal of this ground for rejection.

(iv) The Examiner finds the recitation of "the plurality of classes of polynucleotides" in claims 31 and 44 to lack proper antecedent basis in the "polynucleotide samples" and plurality of samples" recited in claim 28. Claims 31 and 44 have been amended to read "plurality of samples of polynucleotides." Claim 28 specifies "plurality of samples" in subsection (a) and "each sample has polynucleotides" in sub-section (b). Applicants respectfully submit that this amendment provides antecedent basis for the claimed terms of claims 31 and 44 and respectfully request withdrawal of this ground for rejection.

(v) The Examiner finds the recitation of "the mixture of oligonucleotides" in claim 36 to lack proper antecedent basis in the "probe mixture" of claim 28. Claim 36 has been amended to read "the probe mixture of oligonucleotides." Claim 28 specifies that the "probe mixture consist essentially of oligonucleotides." Applicants submit that this amendment provides antecedent basis for the claimed terms of claim 36 and respectfully request withdrawal of this ground for rejection.

Claim Rejections Under 35 U.S.C. § 102

Claims 28-33, 35, 37-44 and 46 stand rejected under 35 U.S.C. § 102(e) as being allegedly anticipated by Fan et al. (U.S. Patent Application No. 2002/0001801 A1, which claims priority of a provisional application filed 16 February 2000).

In response, Applicants traverse this ground for rejection because Fan et al. is not prior art over the current application. Applicants submit herewith the declaration of Mark Schena under 37 C.F.R. §1.31 and accompanying Exhibits A and B (dates redacted) stating that the invention claimed in the instant application was conceived prior to February 16, 2000 (Exhibit A) and diligently reduced to practice until it was filed on July 10, 2000 (Exhibit B). Thus Fan et al. is not prior art over the current application. Withdrawal of this ground for rejection over Fan et al. is respectfully requested.

Further, Applicants submit that the Fan et al. publication is not 102(e) prior art of the instant claims because of the additional reason that Fan et al. do not teach or suggest each and every element of the claims pending in the instant application.

Independent claim 28, as amended, specifies: "the microarray contains a plurality of samples comprising a plurality of genotypes of each individual with each sample in a distinct location."

The Examiner alleges that Fan et al. discloses a microarray that "contains a plurality of samples containing genotypes of interest with each sample in a distinct location (i.e on a bead, paragraph 22)" Office Action at page 5. Applicants respectfully traverse the Examiner's characterization. Fan et al. does not teach a microarray containing a plurality of samples of different genotype with each sample in a distinct location. Fan et al. teach "a population of microspheres comprising *at least a first and second subpopulation*, wherein the microspheres of

each subpopulation each comprise at least first and second target analytes attached to said microspheres . . ." Fan et al., paragraph [0015]. Thus, Fan does not teach a distinct location of each sample. Rather, at least two samples from each individual (e.g., a patient specimen) are attached to a single bead. For example, Fan et al. discloses that "the microspheres of each subpopulation each comprise a plurality of target sequences." Fan et al., paragraph [0016]. Therefore, Applicants submit that Fan et al. does not teach the limitation "each sample in a distinct location" as specified in claim 28.

Further, Fan et al. also do not teach the probe mixture specified in claim 28. Claim 28 specifies, "the oligonucleotides in the probe mixture consist essentially of oligonucleotides of known sequence and length and having sequences specifically complementary to those within the defined segments for each sample for which a genotype is to be determined, wherein the oligonucleotides complementary to the polynucleotides are selected from those with sequences complementary to a segment containing the marker for (1) a gene, (2) one or more allelic variants of the gene, and (3) a gene and one or more allelic variants of the gene, and also consisting essentially of, optionally, control oligonucleotides." (emphasis added.)

Fan et al. teach " a plurality of probes ... used to identify the base at the detection position. ... [E]ach different readout probe comprises a different ... different base at the position that will hybridize to the detection position of the target sequence ... such that differential hybridization will occur. (emphasis added.) That is, all other parameters being equal, a perfectly complementary readout probe (a "match probe") will in general be more stable and have a slower off rate than a probe comprising a mismatch (a "mismatch probe") at any particular temperature." Fan et al. at paragraph [0134].

Fan et al. teach a probe mixture that contains both matched and "mismatched" probes. In contrast, claim 28 specifies a probe mixture **consisting essentially of** oligonucleotides "having sequences specifically complementary to those within the defined segments for each sample." By use of the language "consisting essentially of" claim 28 excludes any mismatched probes. Therefore, Applicants submit that that Fan et al. do not teach this limitation of claim 28.

Claim 28 also specifies that the probe mixture consists essentially of oligonucleotides specifically complementary to "(1) a gene, (2) one or more allelic variants of the gene, and (3) a gene and one or more allelic variants of the gene, and also consisting essentially of, optionally,

control oligonucleotides." Nowhere in the Fan et al. application is disclosed a probe mixture consisting essentially of oligonucleotides as specified in claim 28.

Because Fan et al. fail to teach several limitations of independent claim 28, and claims 29-33, 35, 37-44 and 46 depend from claim 28, Applicants respectfully request that rejection of claims 28-33, 35, 37-44 and 46 over Fan et al. under 35 U.S.C. § 102(e) be withdrawn.

Rejections under 35 U.S.C. § 103(a)

The Examiner has rejected claims 28-39 and 41-46 under 35 U.S.C. 103(a) as being allegedly unpatentable over Drmanac (U.S. Patent No. 6,025,136) in view of Brown et al. (U.S. Patent No. 5,807,522).

Specifically, the Examiner alleges that it would have been obvious "to apply the differentially labeled probes of Brown et al. to the method of Drmanac and to differentially label their marker-specific probes to thereby permit simultaneous detection of multiple samples following a single hybridization step." Office Action at 8.

Applicants respectfully traverse this ground for rejection.

The combination of these references fails to establish a *prima facie* case of obviousness by teaching each and every element of the instant application. The Examiner has characterized the Drmanac reference as teaching a "method comprising multiple rounds of hybridization wherein e.g. a round hybridizes with positive probes and a subsequent round hybridizes with negative probes but Drmanac does not teach detection of the hybrid following a single round of hybridization is indicative of a genotype." Office Action at 7. Thus, by the Examiner's own admission, Drmanac, unlike the instant application, does not teach a single round of hybridization to perform genotyping. Instead, Drmanac teaches a diagnostic method for scoring known mutations that employs five probes per allele in three cycles of hybridization. Drmanac, Example 6, column 7, lines 29-45. In contrast, Applicant's method specifies that the formation of a hybrid (or lack therof) after a single round of hybridization is indicative of the genotype of a particular sample on the microarray.

Furthermore, Drmanac teaches the use of universal sets of probes. As taught in Example 1 of the Drmanac reference, "[t]he first [set of probes] is a complete set (or at least a *noncomplementary* subset) of relatively short probes. For example, all 4096 (or about 2000 non-complementary) 6-mers, or all 16,384 (or about 8,000 *non-complimentary*) 7-mers." (emphasis added). The disclosure of the oligonucleotide mixture in Drmanac teaches away from the oligonucleotide mixture taught in the instant application.

In contrast to the teaching of Drmanac, claim 28 of the instant application claims, in part, "the oligonucleotides in the probe mixture consist essentially of oligonucleotides of known sequence and length and having sequences specifically complementary to those within the defined segments for each sample for which a genotype is to be determined." (emphasis added). Further, Applicants have claimed the probe mixture of oligonucleotides in terms of "consist essentially of" thereby excluding oligonucleotides not specified in the claim.

Further, Drmanac does not teach or suggest a probe mixture of oligonucleotides "wherein the oligonucleotides complementary to the polynucleotides are selected from those with sequences complementary to a segment containing the marker for (1) a gene, (2) one or more allelic variants of the gene, and (3) a gene and one or more allelic variants of the gene, and also consisting essentially of, optionally, control oligonucleotides" as specified in claim 28.

The Examiner contends that Brown et al. teach "a similar method of simultaneously genotyping multiple samples comprising: incubating a microarray of polynucleotide samples from multiple individuals with a probe mixture wherein the microarray contains a plurality of samples containing geneotypes of interest (amplified region of interest), each sample having polynucleotides with a defined segment containing a marker (region of interest) and the probes consist of oligonucleotides complementary to the regions of interest, the incubating forms hybrids and allows discrimination at a single nucleotide resolution (i.e. perfect match) and detecting stable hybrids following a single round of hybridization which is indicative of genotype (column 15, lines 19-52)." The Examiner asserts that Brown et al. further teach that their method wherein differentially labeled probes detected following a single hybridization

permits simultaneous detection of the pluraity of samples with "significant time and cost savings." (Column 15, lines 13-16, 39-43 and 52-67). Office Action at 8.

Contrary to the Examiner's suggestion, Brown et al. does not teach the elements of the instant claimed invention. Specifically, Brown et al. teach the use of "96 identical 0.9 cm x 2.2 cm microarrays fabricated on a single 12 cm x 18 cm sheet of plastic-backed nitrocellulose where each microarray could contain, for example, 100 DNA fragments representing all known mutations of a given gene." Brown et al., column 15, lines 22-27. Thus, Brown et al. teach multiple microarrays. Brown et al. then teach the hybridization of the 96 microarrrays with 96 patient samples, with the 96 individual microarrays separated from each other by silicone rubber barrier elements. Thus, Brown et al. teach multiple hybridizations.

In brief, Brown et al. teach the use of a single sheet with multiple arrays that are subject to separate hybridization events, not a single round of hybridization on a single microarray as in the instant application.

Additionally, although Brown et al. teach that "the array format can be reversed where the patient or organism's DNA is immobilized as the array elements", the specification further teaches that "each array is hybridized with a different mutated allele or genetic marker." Brown et al., column 15, lines 44-47. (emphasis added). Thus, again, Brown et al. teach the use of multiple rounds of hybridization on multiple arrays, not a single round as in the instant application.

Furthermore, Brown et al. does not teach the probe mixture specified in claim 28 which states: "oligonucleotides of known sequence and length and having sequences specifically complementary to those within the defined segments for each sample for which a genotype is to be determined," and the oligonucleotides are "selected from those with sequences complementary to a segment containing the marker for (1) a gene, (2) one or more allelic variants of the gene, and (3) a gene and one or more allelic variants of the gene, and also consisting essentially of, optionally, control oligonucleotides." (emphasis added.)

In contrast to the probe mixture claimed in Claim 28, Brown et al. teach generally, that the probes for the microarrays are mixtures of labelled cDNAs that are prepared from total mRNA (Column 4, lines 52-64). Brown et al. teach that in genotyping studies, the arrays containing gene segments are to be probed with complex mixtures of largely unknown composition (e.g. cDNA from total mRNA or total DNA from a patient). See Brown et al. column 14, line 55 to column 15, line 4.

Applicants submit that neither Brown et al. nor Drmanac teach or suggest determination of the genotypes of multiple samples by a single round of hybridization using the probe mixture specified in claim 28. The Examiner has not pointed to any teaching or suggestion to combine the teachings of Drmanac and Brown or how such combination would lead to the probe mixture specified in claim 28. Since Drmanac and Brown et al., individually or in combination, do not teach each and every element of independent claim 28, and claims 29-46 depend from claim 28, Applicants respectfully request that the rejection based on 35 U.S.C. § 103(a) be withdrawn.

The Examiner has rejected claim 40 under 35 U.S.C. § 103(a) as being allegedly unpatentable over Drmanac (U.S. Patent No. 6,025,136) in view of Brown et al. (U.S. Patent No. 5,807,522) as applied to claim 28 and further in view of Hames et al. (Nucleic Acid Hybridization: a practical approach, IRL Press, Washington DC, 1985, pages 105-108).

Hames is cited by the Examiner for teaching hybridization at a temperature 10 degrees below stable hybrid melting temperature. In response, Applicants note that claim 40 depends from independent claim 28. As discussed above, Drmanac and Brown et al., individually or in combination, do not teach each and every element of claim 28. Since a combination of Drmanac, Brown et al. and Hames do not teach each and every element of claim 40, Applicants respectfully request withdrawal of this ground for rejection of claim 40 under 35 U.S.C. § 103(a).

CONCLUSION

Applicants have, by way of the amendments and remarks presented herein addressed all issues that were raised in the outstanding Office Action. In light of the Amendments and the arguments set forth above, Applicants earnestly believe that they are entitled to a letters patent, and respectfully solicit the Examiner to expedite prosecution of this patent application to issuance. If it is determined that a telephone conversation would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant(s) petition(s) for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 529492000100.

Respectfully submitted,

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